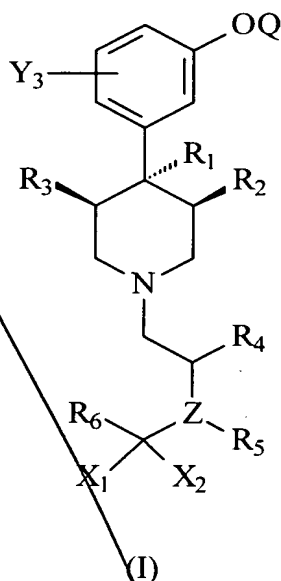


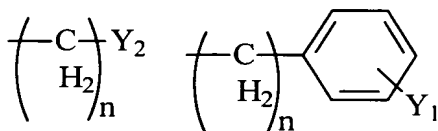
Claims:

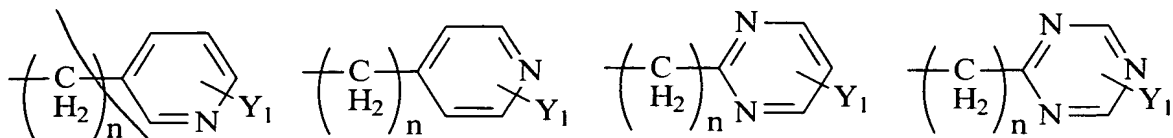
1. A method of binding a kappa opioid receptor in a subject in need thereof, comprising:
- administering to said subject a composition comprising a kappa opioid receptor antagonist and a physiologically acceptable carrier, wherein the kappa opioid receptor antagonist is a compound of formula (I):



wherein Q is H or COC₁₋₈ alkyl;

R₁ is C₁₋₈ alkyl, or one of the following structures:





Y₁ is H, OH, Br, Cl, F, CN, CF₃, NO₂, N₃, OR₈, CO₂R₉, C₁₋₆ alkyl, NR₁₀R₁₁, NHCOR₁₂, NHCO₂R₁₂, CONR₁₃R₁₄, CH₂(CH₂)_nY₂;

Y₂ is H, CF₃, CO₂R₉, C₁₋₆alkyl, NR₁₀R₁₁, NHCOR₁₂, NHCO₂R₁₂, CONR₁₃R₁₄, CH₂OH, CH₂OR₈, COCH₂R₉;

Y₃ is H, OH, Br, Cl, F, CN, CF₃, NO₂, N₃, OR₈, CO₂R₉, C₁₋₆ alkyl, NR₁₀R₁₁, NHCOR₁₂, NHCO₂R₁₂, CONR₁₃R₁₄, CH₂(CH₂)_nY₂;

R₂ is H, C₁₋₈ alkyl, C₃₋₈ alkenyl, C₃₋₈ alkynyl or CH₂aryl substituted by one or more groups Y₁;

R₃ is H, C₁₋₈ alkyl, C₃₋₈ alkenyl, C₃₋₈ alkynyl or CH₂aryl substituted by one or more groups Y₁;

wherein R₂ and R₃ may be bonded together to form a C₂₋₈ alkyl group;

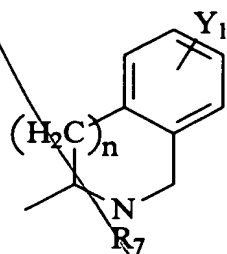
R₄ is hydrogen, C₁₋₈ alkyl, CO₂C₁₋₈ alkylaryl substituted by one or more groups Y₁, CH₂aryl substituted by one or more groups Y₁, or CO₂C₁₋₈ alkyl;

Z is N, O or S; where Z is O or S, there is no R₅

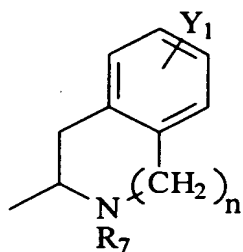
R₅ is H, C₁₋₈ alkyl, C₃₋₈ alkenyl, C₃₋₈ alkynyl, CH₂CO₂C₁₋₈ alkyl, CO₂C₁₋₈ alkyl or CH₂aryl substituted by one or more groups Y₁;

n is 0, 1, 2 or 3;

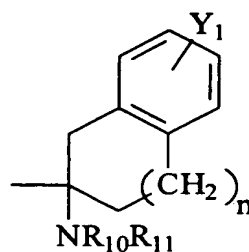
R₆ is a group selected from the group consisting of structures (a)-(bbb):



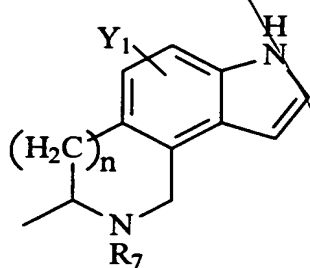
(a)



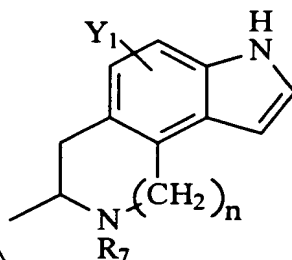
(b)



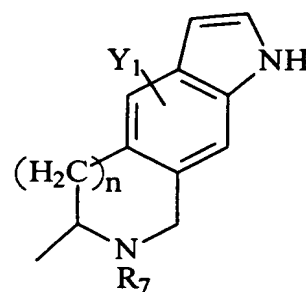
(c)



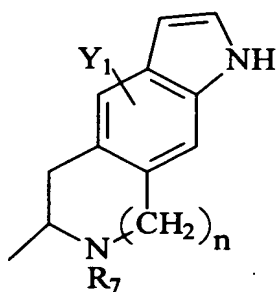
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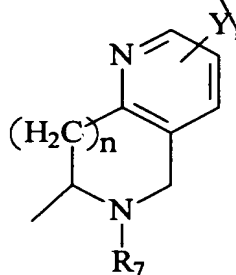
(e)



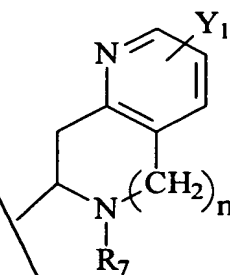
(f)



(g)



(h)



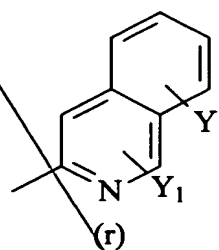
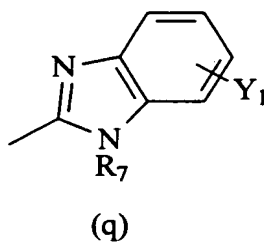
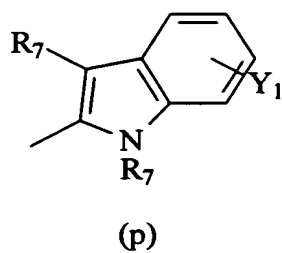
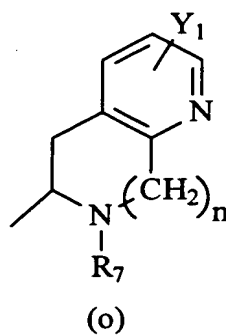
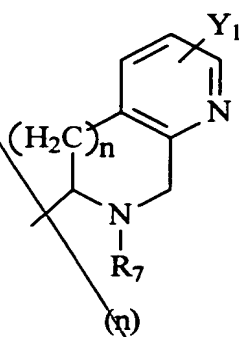
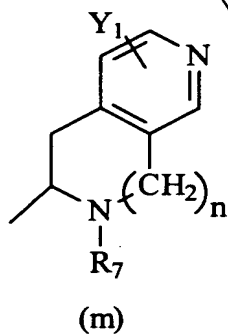
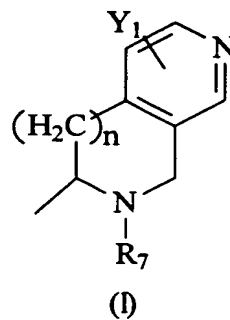
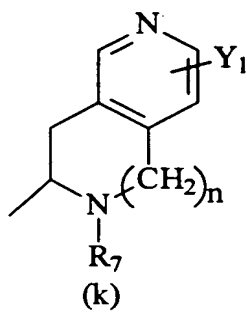
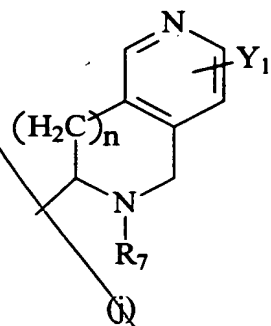
(i)

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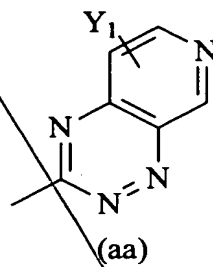
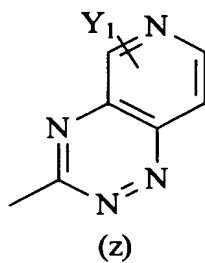
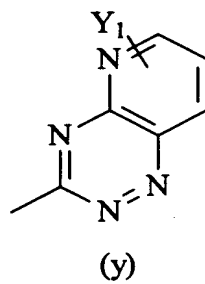
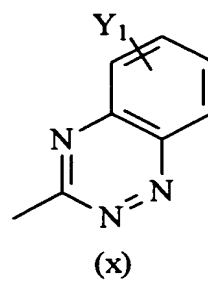
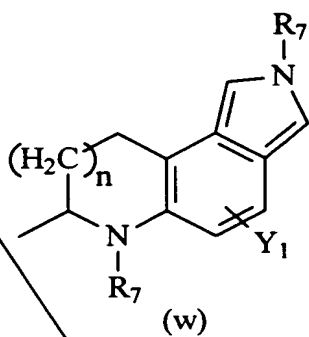
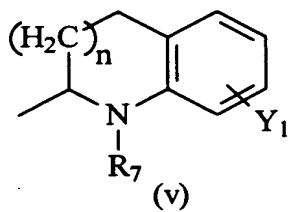
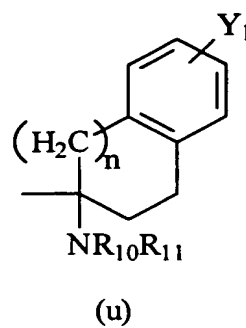
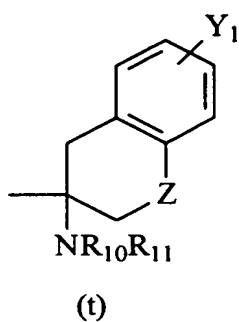
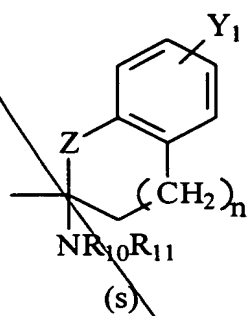
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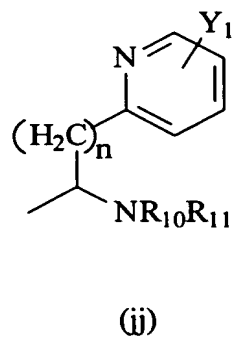
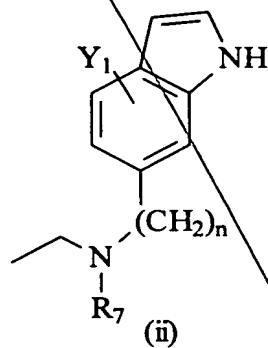
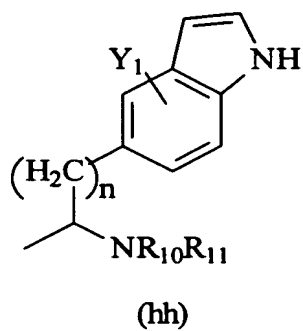
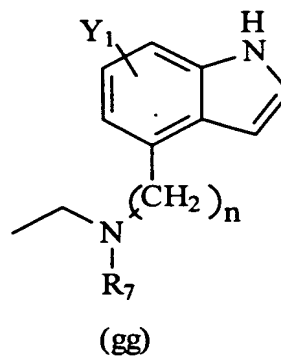
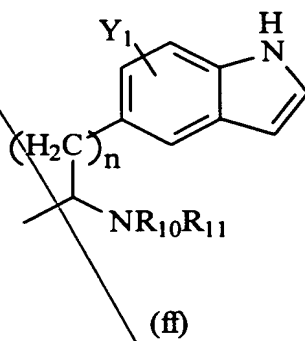
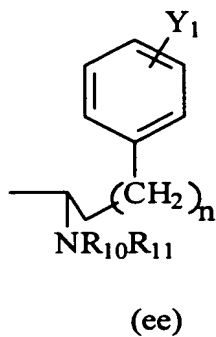
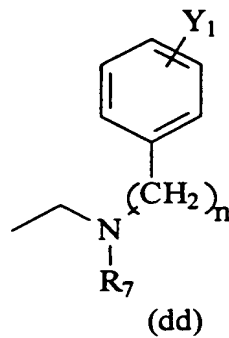
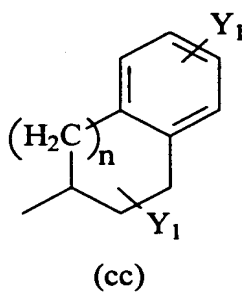
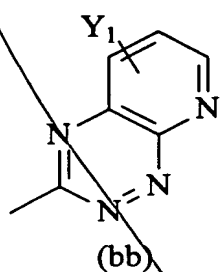
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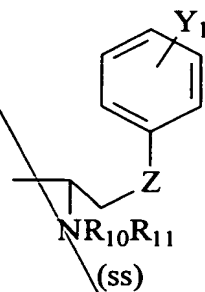
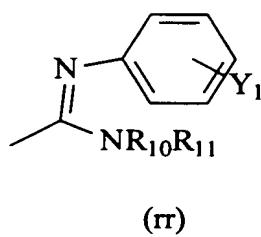
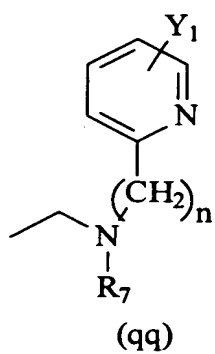
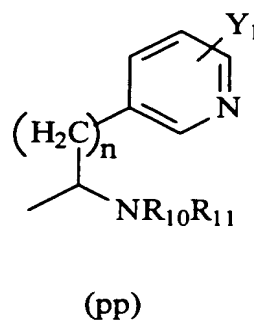
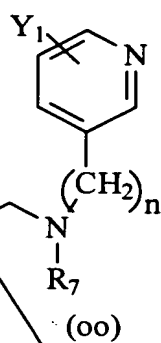
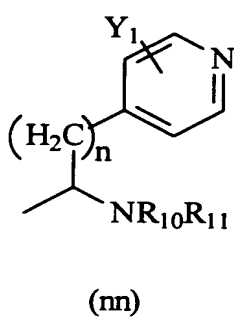
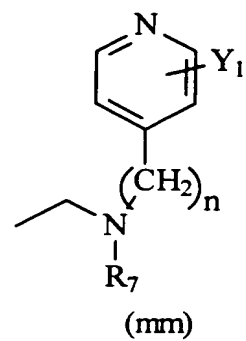
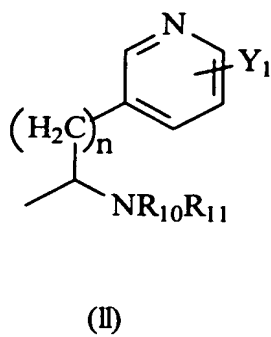
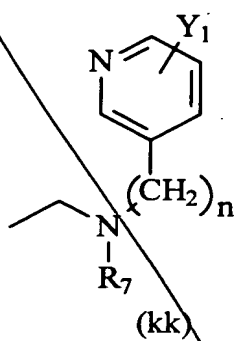
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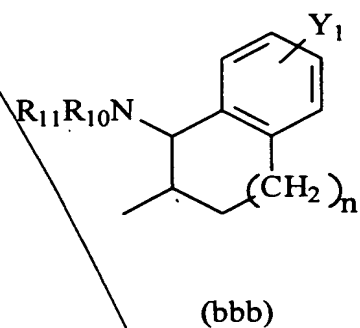
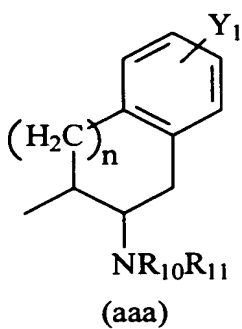
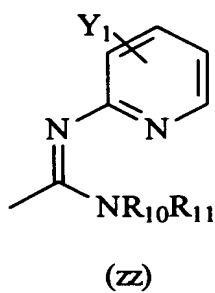
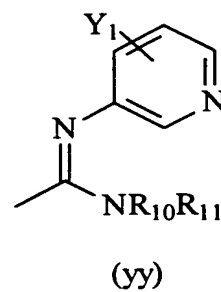
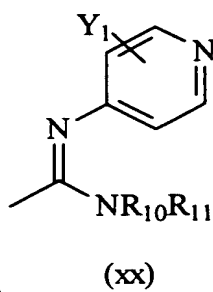
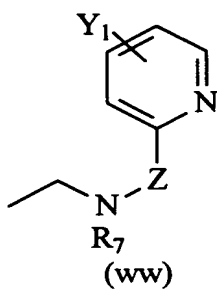
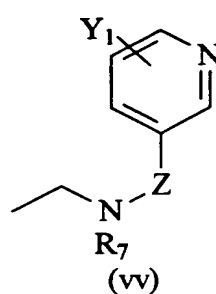
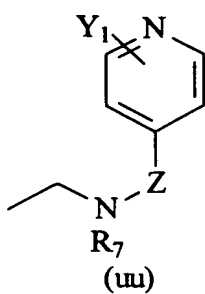
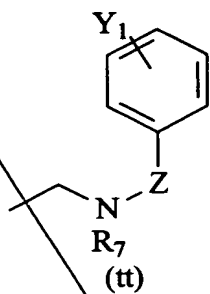
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X₁ is hydrogen, C₁₋₈ alkyl, C₃₋₈alkenyl, C₃₋₈alkynyl;

X₂ is hydrogen, C₁₋₈alkyl, C₃₋₈alkenyl, C₃₋₈alkynyl;

or X₁ and X₂ together form =O, =S, =NH;

R₇ is H, C₁₋₈alkyl, CH₂aryl substituted by one or more substituents Y₁, NR₁₀R₁₁,

5 NHCOR₁₂, NHCO₂R₁₃, CONR₁₄R₁₅, CH₂(CH₂)_nY₂, C(=NH)NR₁₆R₁₇.

R₈ is H, C₁₋₈alkyl, CH₂aryl substituted by one or more substituents Y₁, CONR₁₃R₁₄,
CH₂(CH₂)_nY₂.

R₉ is H, C₁₋₈ alkyl, CH₂ aryl substituted by one or more substituents Y₁, CH₂(CH₂)_nY₂;

R₁₀ is H, C₁₋₈ alkyl, CH₂ aryl substituted by one or more substituents Y₁, CH₂(CH₂)_nY₂;

R₁₁ is H, C₁₋₈ alkyl, CH₂ aryl substituted by one or more substituents Y₁, CH₂(CH₂)_nY₂;

R₁₂ is H, C₁₋₈ alkyl, CH₂ aryl substituted by one or more substituents Y₁, CH₂(CH₂)_nY₂;

R₁₃ is H, C₁₋₈ alkyl, CH₂ aryl substituted by one or more substituents Y₁, CH₂(CH₂)_nY₂;

R₁₄ is H, C₁₋₈ alkyl, CH₂ aryl substituted by one or more substituents Y₁, CH₂(CH₂)_nY₂;

R₁₅ is H, C₁₋₈ alkyl, CH₂ aryl substituted by one or more substituents Y₁, CH₂(CH₂)_nY₂;

R₁₆ is H, C₁₋₈ alkyl, CH₂ aryl substituted by one or more substituents Y₁, CH₂(CH₂)_nY₂;

and

R₁₇ is H, C₁₋₈ alkyl, CH₂ aryl substituted by one or more substituents Y₁, CH₂(CH₂)_nY₂.

2. The method of claim 1, wherein said kappa opioid receptor antagonist is a
compound of formula (I), wherein R₁, R₄, R₅, Y₁, Y₂, Z, n, X₁, X₂, and R₇-R₁₇ are as indicated
above;

Y₃ is H;

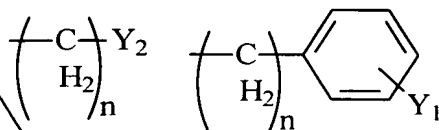
R₂ and R₃ are each, independently, H, C₁₋₈ alkyl, C₃₋₈ alkenyl, C₃₋₈ alkynyl, CH₂aryl
substituted by one or more substituents Y₁; and

R₆ is a group having a formula selected from the group consisting of structures (a)-
(cc).

and pharmaceutically acceptable salts thereof.

3. The method of claim 1, wherein said kappa opioid receptor antagonist is a
compound of formula (I) wherein Y₁, Y₂, R₄, R₅, Z, n, X₁, X₂ and R₈-R₁₅ are as indicated
above;

R₁ is C₁₋₈ alkyl,



Y₃ is H;

R₂ and R₃ are each, independently, H or C₁₋₈ alkyl, wherein R₂ and R₃ cannot both be H at the same time;

R₆ is a formula selected from the structures (a)-(r); and

R₇ is H, C₁₋₈ alkyl, CH₂aryl substituted by one or more substituents Y₁, NR₁₀R₁₁, NHCOR₁₂, NHCO₂R₁₃, CONR₁₄R₁₅, or CH₂(CH₂)_nY₂.

4. The method of claim 1, wherein said kappa opioid receptor antagonist is a compound of formula (I) wherein Y₁, Z, n, X₁, X₂ and R₈-R₁₅ are as noted above;

R₁ is C₁₋₈ alkyl;

Y₂ is H, CF₃, CO₂R₉, C₁₋₆ alkyl, NR₁₀R₁₁, NHCOR₁₂, NHCO₂R₁₂, CONR₁₃R₁₄, CH₂OH, CH₂OR₈, COCH₂R₉;

Y₃ is H;

R₂ and R₃ are each, independently, H or methyl, wherein R₂ and R₃ cannot both be H at the same time;

15 R₄ is H, C₁₋₈ alkyl, CO₂C₁₋₈alkyl, aryl substituted by one or more substituents Y₁ and the stereocenter adjacent to R₄ is in an (S) configuration;

R₅ is H, C₁₋₈ alkyl, CH₂CO₂C₁₋₈ alkyl;

R₆ is a group having a formula selected from the group consisting of structures (a)-(c) and (h)-(o); and

20 R₇ is H, C₁₋₈alkyl, CH₂aryl substituted by one or more substituents Y₁, NR₁₀R₁₁, NHCOR₁₂, NHCO₂R₁₃, CONR₁₄R₁₅, or CH₂(CH₂)_nY₂.

5. The method of claim 1, wherein said kappa opioid receptor antagonist is a compound of formula (I), wherein Y₁, Z, n, X₁, X₂ and R₈-R₁₄ are as indicated above;

R_1 is methyl,

Y_2 is H, CF_3 , CO_2R_9 , C_{1-6} alkyl, $NR_{10}R_{11}$, $NHCO_2R_{12}$, $NHCO_2R_{12}$, $CONR_{13}R_{14}$,
 CH_2OH , CH_2OR_8 , $COCH_2R_9$;

Y_3 is H;

R_2 and R_3 are each H or methyl, such that when R_2 is H, R_3 is methyl and vice versa;

R_4 is C_{1-8} alkyl, CO_2C_{1-8} alkyl, and the stereocenter adjacent to R_4 has a configuration
of (S);

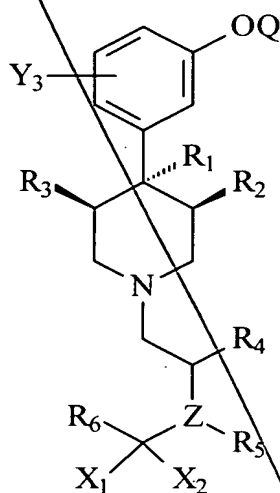
R_5 is H;

R_6 is a group having a formula selected from the group consisting of structures (a) and
(b); and

R_7 is H, C_{1-8} alkyl, CH_2 aryl substituted by one or more substituents Y_1 or
 $CH_2(CH_2)_nY_2$.

6. The method of claim 1, wherein said kappa opioid receptor antagonist is a
compound selected from formulae 14-21 of Fig. 1.

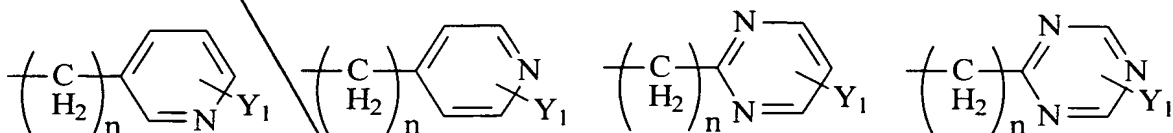
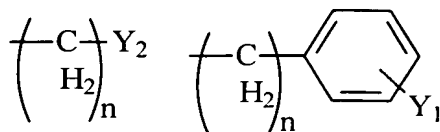
7. A kappa opioid receptor antagonist compound represented by the formula (I):



(I)

wherein Q is H or COC_{1-8} alkyl;

R_1 is C_{1-8} alkyl, or one of the following structures:



Y₁ is H, OH, Br, Cl, F, CN, CF₃, NO₂, N₃, OR₈, CO₂R₉, C₁₋₆ alkyl, NR₁₀R₁₁, NHCOR₁₂, NHCO₂R₁₂, CONR₁₃R₁₄, CH₂(CH₂)_nY₂;

Y₂ is H, CF₃, CO₂R₉, C₁₋₆ alkyl, NR₁₀R₁₁, NHCOR₁₂, NHCO₂R₁₂, CONR₁₃R₁₄, CH₂OH, CH₂OR₈, COCH₂R₉;

Y₃ is H, OH, Br, Cl, F, CN, CF₃, NO₂, N₃, OR₈, CO₂R₉, C₁₋₆ alkyl, NR₁₀R₁₁, NHCOR₁₂, NHCO₂R₁₂, CONR₁₃R₁₄, CH₂(CH₂)_nY₂;

R₂ is H, C₁₋₈ alkyl, C₃₋₈ alkenyl, C₃₋₈ alkynyl or CH₂aryl substituted by one or more groups Y₁;

R₃ is H, C₁₋₈ alkyl, C₃₋₈ alkenyl, C₃₋₈ alkynyl or CH₂aryl substituted by one or more groups Y₁;

wherein R₂ and R₃ may be bonded together to form a C₂₋₈ alkyl group;

R₄ is hydrogen, C₁₋₈ alkyl, CO₂C₁₋₈ alkylaryl substituted by one or more groups Y₁, CH₂aryl substituted by one or more groups Y₁ or CO₂C₁₋₈ alkyl;

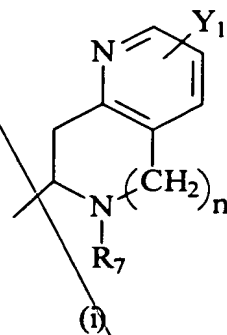
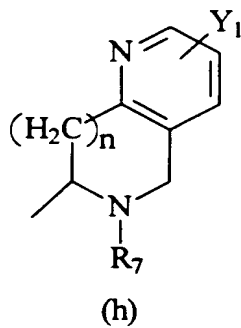
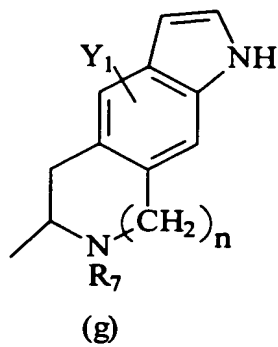
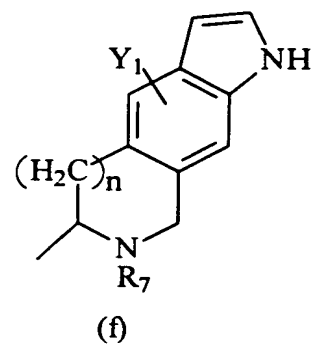
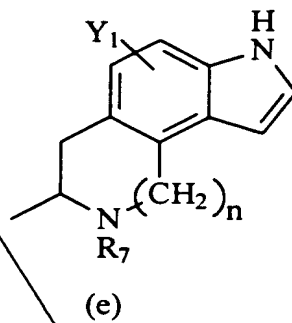
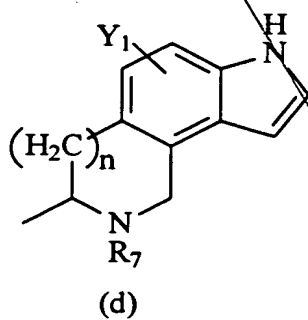
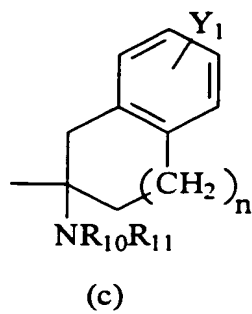
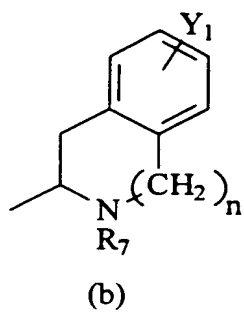
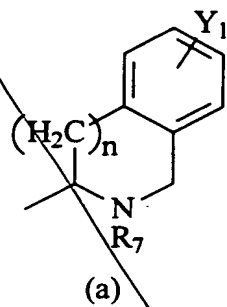
Z is N, O or S; when Z is O or S there is no R₅;

R₅ is H, C₁₋₈ alkyl, C₃₋₈ alkenyl, C₃₋₈ alkynyl, CH₂CO₂C₁₋₈ alkyl, CO₂C₁₋₈ alkyl or CH₂aryl substituted by one or more groups Y₁;

n is 0, 1, 2 or 3;

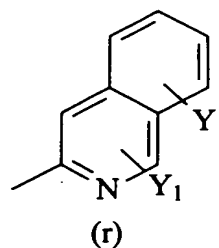
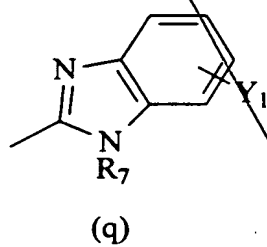
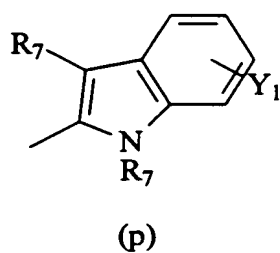
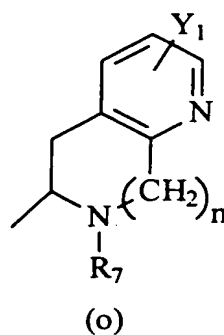
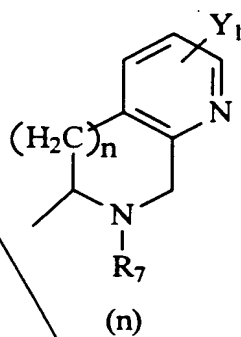
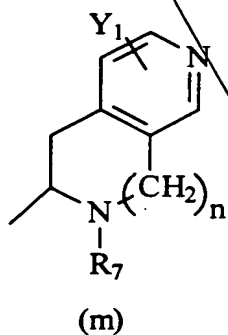
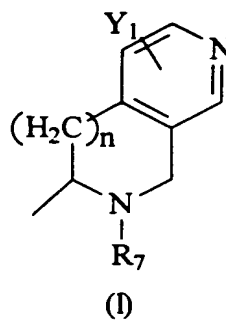
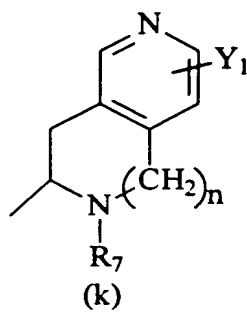
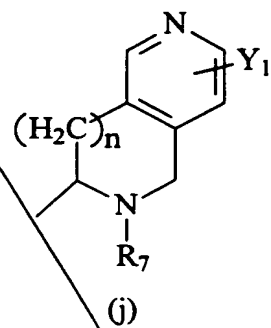
R₆ is a group selected from the group consisting of structures (a)-(bbb):

Year	1955	1956	1957	1958	1959	1960	1961	1962	1963	1964	1965	1966	1967	1968	1969	1970	1971	1972	1973	1974	1975	1976	1977	1978	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042	2043	2044	2045	2046	2047	2048	2049	2050	2051	2052	2053	2054	2055	2056	2057	2058	2059	2060	2061	2062	2063	2064	2065	2066	2067	2068	2069	2070	2071	2072	2073	2074	2075	2076	2077	2078	2079	2080	2081	2082	2083	2084	2085	2086	2087	2088	2089	2090	2091	2092	2093	2094	2095	2096	2097	2098	2099	2100																																			
Population	1000000	1050000	1100000	1150000	1200000	1250000	1300000	1350000	1400000	1450000	1500000	1550000	1600000	1650000	1700000	1750000	1800000	1850000	1900000	1950000	2000000	2050000	2100000	2150000	2200000	2250000	2300000	2350000	2400000	2450000	2500000	2550000	2600000	2650000	2700000	2750000	2800000	2850000	2900000	2950000	3000000	3050000	3100000	3150000	3200000	3250000	3300000	3350000	3400000	3450000	3500000	3550000	3600000	3650000	3700000	3750000	3800000	3850000	3900000	3950000	4000000	4050000	4100000	4150000	4200000	4250000	4300000	4350000	4400000	4450000	4500000	4550000	4600000	4650000	4700000	4750000	4800000	4850000	4900000	4950000	5000000	5050000	5100000	5150000	5200000	5250000	5300000	5350000	5400000	5450000	5500000	5550000	5600000	5650000	5700000	5750000	5800000	5850000	5900000	5950000	6000000	6050000	6100000	6150000	6200000	6250000	6300000	6350000	6400000	6450000	6500000	6550000	6600000	6650000	6700000	6750000	6800000	6850000	6900000	6950000	7000000	7050000	7100000	7150000	7200000	7250000	7300000	7350000	7400000	7450000	7500000	7550000	7600000	7650000	7700000	7750000	7800000	7850000	7900000	7950000	8000000	8050000	8100000	8150000	8200000	8250000	8300000	8350000	8400000	8450000	8500000	8550000	8600000	8650000	8700000	8750000	8800000	8850000	8900000	8950000	9000000	9050000	9100000	9150000	9200000	9250000	9300000	9350000	9400000	9450000	9500000	9550000	9600000	9650000	9700000	9750000	9800000	9850000	9900000	9950000	10000000



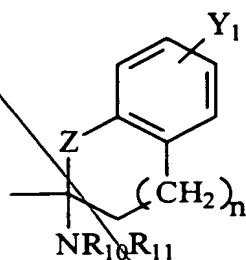
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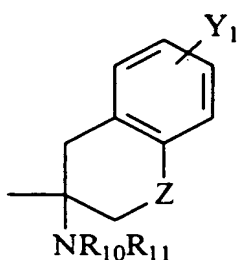


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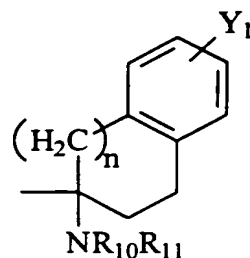
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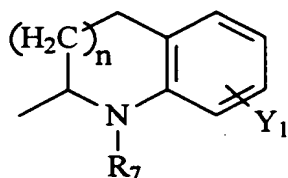
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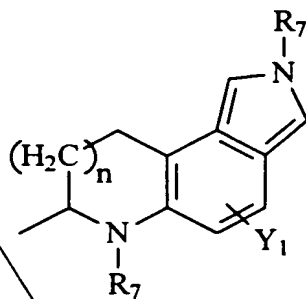
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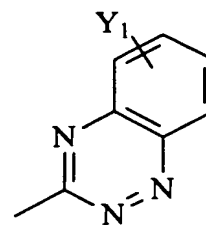
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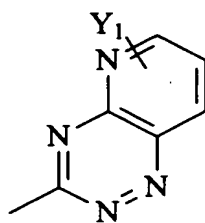
(v)



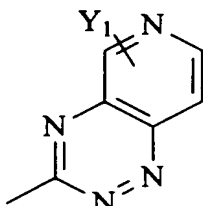
(w)



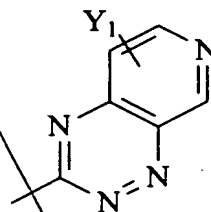
(x)



(y)



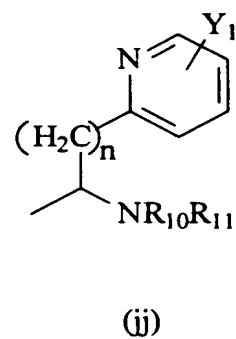
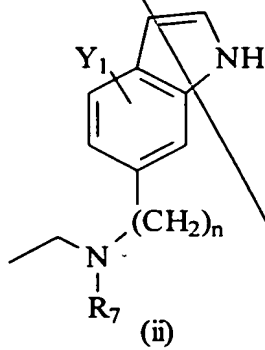
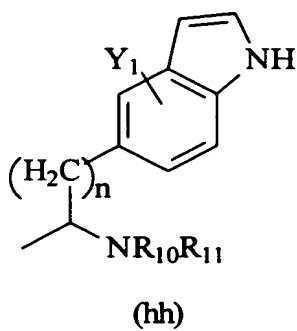
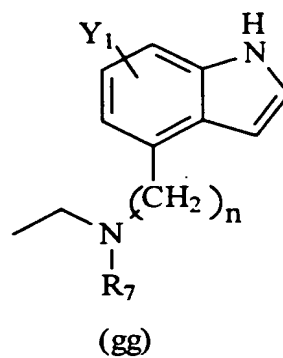
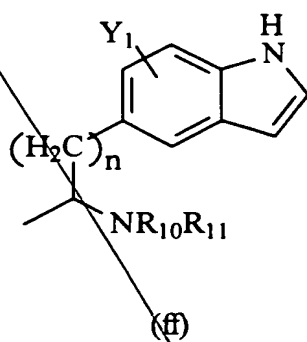
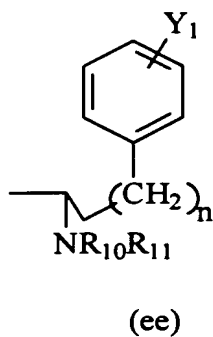
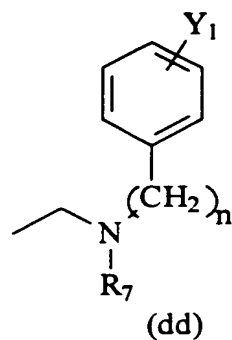
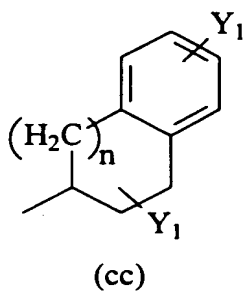
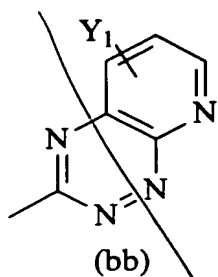
(z)



(aa)

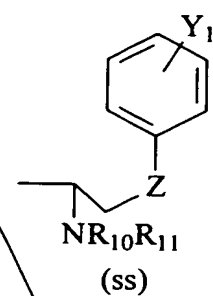
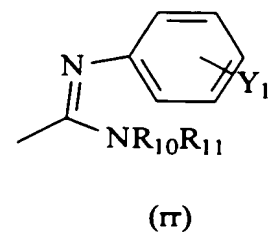
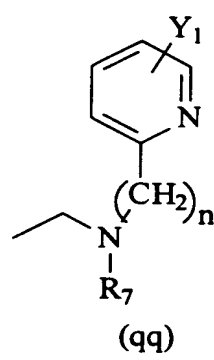
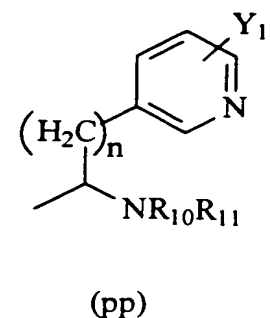
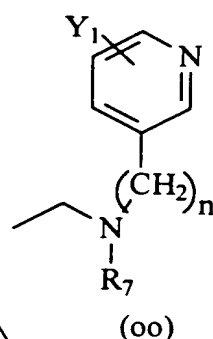
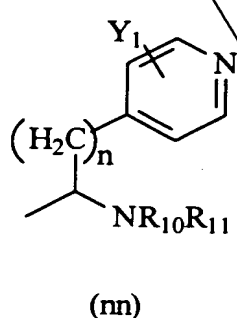
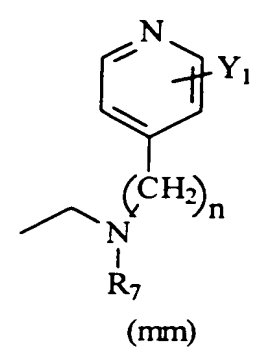
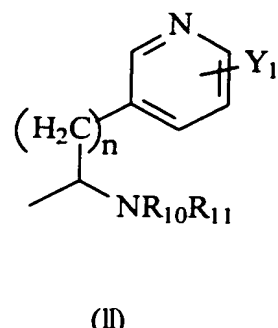
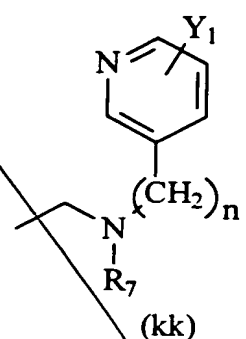
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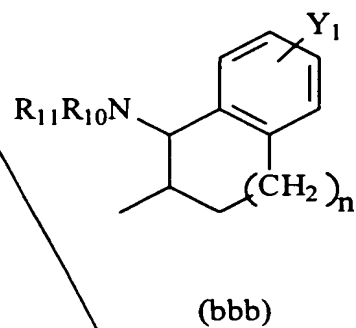
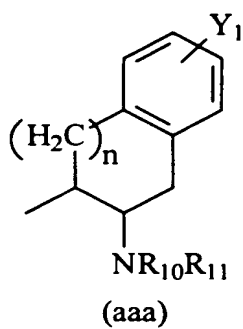
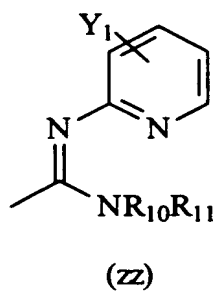
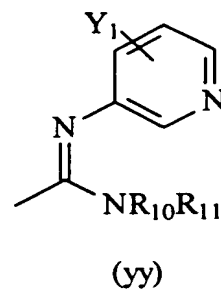
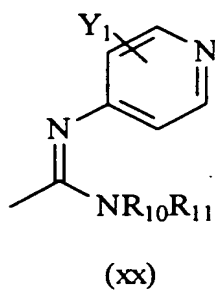
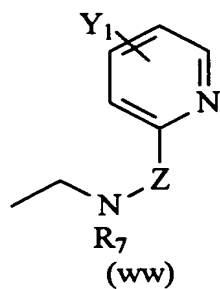
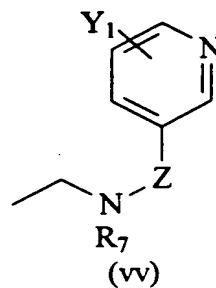
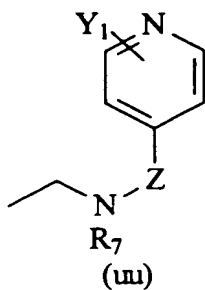
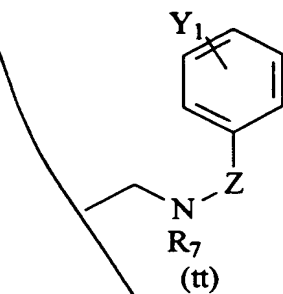
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X_1 is hydrogen, C_{1-8} alkyl, C_{3-8} alkenyl, C_{3-8} alkynyl;

X_2 is hydrogen, C_{1-8} alkyl, C_{3-8} alkenyl, C_{3-8} alkynyl;

or X_1 and X_2 together form $=O$, $=S$, $=NH$;

R_7 is H, C_{1-8} alkyl, CH_2 aryl substituted by one or more substituents Y_1 , $NR_{10}R_{11}$,

5 $NHCO R_{12}$, $NHCO_2 R_{13}$, $CONR_{14}R_{15}$, $CH_2(CH_2)_n Y_2$, $C(=NH)NR_{16}R_{17}$;

R_8 is H, C_{1-8} alkyl, CH_2 aryl substituted by one or more substituents Y_1 , $CONR_{13}R_{14}$,
 $CH_2(CH_2)_n Y_2$;

R_9 is H, C_{1-8} alkyl, CH_2 aryl substituted by one or more substituents Y_1 , $CH_2(CH_2)_n Y_2$;

R_{10} is H, C_{1-8} alkyl, CH_2 aryl substituted by one or more substituents Y_1 , $CH_2(CH_2)_n Y_2$;

R_{11} is H, C_{1-8} alkyl, CH_2 aryl substituted by one or more substituents Y_1 , $CH_2(CH_2)_n Y_2$;

R_{12} is H, C_{1-8} alkyl, CH_2 aryl substituted by one or more substituents Y_1 , $CH_2(CH_2)_n Y_2$;

R_{13} is H, C_{1-8} alkyl, CH_2 aryl substituted by one or more substituents Y_1 , $CH_2(CH_2)_n Y_2$;

R_{14} is H, C_{1-8} alkyl, CH_2 aryl substituted by one or more substituents Y_1 , $CH_2(CH_2)_n Y_2$;

R_{15} is H, C_{1-8} alkyl, CH_2 aryl substituted by one or more substituents Y_1 , $CH_2(CH_2)_n Y_2$;

R_{16} is H, C_{1-8} alkyl, CH_2 aryl substituted by one or more substituents Y_1 , $CH_2(CH_2)_n Y_2$;

and

R_{17} is H, C_{1-8} alkyl, CH_2 aryl substituted by one or more substituents Y_1 , $CH_2(CH_2)_n Y_2$
and pharmaceutically acceptable salts thereof.

8. The kappa opioid receptor antagonist compound of claim 7, wherein R_1 , R_4 , R_5 , Y_1 ,
20 Y_2 , Z , n , X_1 , X_2 , and R_7 - R_{17} are as indicated above;

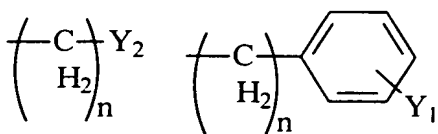
Y_3 is H;

R_2 and R_3 are each, independently, H, C_{1-8} alkyl, C_{3-8} alkenyl, C_{3-8} alkynyl, CH_2 aryl
substituted by one or more substituents Y_1 ; and

R_6 is a group having a formula selected from the group consisting of structures (a)-
25 (cc).

9. The kappa opioid receptor antagonist compound of claim 7, wherein Y_1 , Y_2 , R_4 , R_5 ,
 Z , n , X_1 , X_2 and R_8 - R_{15} are as indicated above;

R_1 is C_{1-8} alkyl,



Y₃ is H;

R₂ and R₃ are each, independently, H or C₁₋₈ alkyl, wherein R₂ and R₃ cannot both be H at the same time;

R₆ is a formula selected from the structures (a)-(r) shown above; and

R₇ is H, C₁₋₈ alkyl, CH₂aryl substituted by one or more substituents Y₁, NR₁₀R₁₁, NHCOR₁₂, NHCO₂R₁₃, CONR₁₄R₁₅, or CH₂(CH₂)_nY₂.

10. The kappa opioid receptor antagonist compound of claim 7, wherein Y₁, Z, n, X₁, X₂ and R₈-R₁₅ are as noted above;

R₁ is C₁₋₈ alkyl;

Y₂ is H, CF₃, CO₂R₉, C₁₋₆ alkyl, NR₁₀R₁₁, NHCOR₁₂, NHCO₂R₁₂, CONR₁₃R₁₄, CH₂OH, CH₂OR₈, COCH₂R₉;

Y₃ is H;

R₂ and R₃ are each, independently, H or methyl, wherein R₂ and R₃ cannot both be H at the same time;

R₄ is H, C₁₋₈ alkyl, CO₂C₁₋₈alkyl, aryl substituted by one or more substituents Y₁ and the stereocenter adjacent to R₄ is in an (S) configuration;

R₅ is H, C₁₋₈ alkyl, CH₂CO₂C₁₋₈ alkyl;

R₆ is a group having a formula selected from the group consisting of structures (a)-(c) and (h)-(o); and

R₇ is H, C₁₋₈alkyl, CH₂aryl substituted by one or more substituents Y₁, NR₁₀R₁₁, NHCOR₁₂, NHCO₂R₁₃, CONR₁₄R₁₅, or CH₂(CH₂)_nY₂.

11. The kappa opioid receptor antagonist compound of claim 7, wherein Y₁, Z, n, X₁, X₂ and R₈-R₁₄ are as indicated above;

R₁ is methyl,

Y₂ is H, CF₃, CO₂R₉, C₁₋₆ alkyl, NR₁₀R₁₁, NHCOR₁₂, NHCO₂R₁₂, CONR₁₃R₁₄, CH₂OH, CH₂OR₈, COCH₂R₉;

Y₃ is H;

R₂ and R₃ are each H or methyl, such that when R₂ is H, R₃ is methyl and vice versa;

R_4 is C_{1-8} alkyl, CO_2C_{1-8} alkyl, and the stereocenter adjacent to R_4 has a configuration of (S);

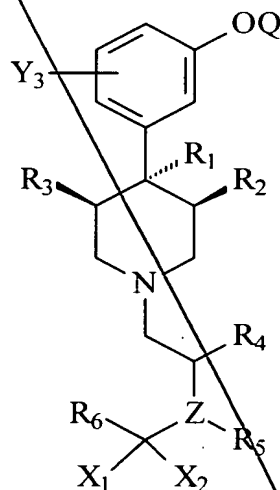
R_5 is H;

R_6 is a group having a formula selected from the group consisting of structures (a) and (b); and

R_7 is H, C_{1-8} alkyl, CH_2 aryl substituted by one or more substituents Y_1 or $CH_2(CH_2)_nY_2$.

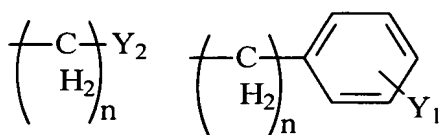
12. The kappa opioid receptor antagonist of claim 7, wherein said compound is a compound selected from formulae **14-21** of Fig. 1.

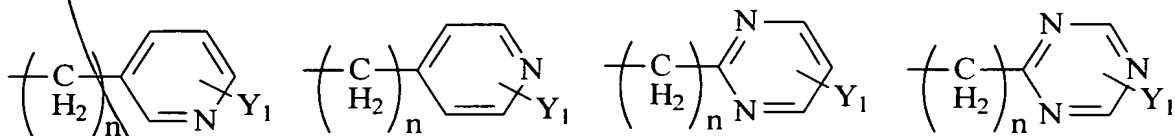
13. A pharmaceutical composition comprising:
an effective amount of a kappa opioid receptor antagonist and a physiologically acceptable carrier, wherein the kappa opioid receptor antagonist is a compound of formula (I):



wherein Q is H or $CO C_{1-8}$ alkyl;

R_1 is C_{1-8} alkyl, or one of the following structures:





Y₁ is H, OH, Br, Cl, F, CN, CF₃, NO₂, N₃, OR₈, CO₂R₉, C₁₋₆ alkyl, NR₁₀R₁₁, NHCOR₁₂, NHCO₂R₁₂, CONR₁₃R₁₄, CH₂(CH₂)_nY₂;

Y₂ is H, CF₃, CO₂R₉, C₁₋₆alkyl, NR₁₀R₁₁, NHCOR₁₂, NHCO₂R₁₂, CONR₁₃R₁₄, CH₂OH, CH₂OR₈, COCH₂R₉;

Y₃ is H, OH, Br, Cl, F, CN, CF₃, NO₂, N₃, OR₈, CO₂R₉, C₁₋₆ alkyl, NR₁₀R₁₁, NHCOR₁₂, NHCO₂R₁₂, CONR₁₃R₁₄, CH₂(CH₂)_nY₂;

R₂ is H, C₁₋₈ alkyl, C₃₋₈ alkenyl, C₃₋₈ alkynyl or CH₂aryl substituted by one or more groups Y₁;

R₃ is H, C₁₋₈ alkyl, C₃₋₈ alkenyl, C₃₋₈ alkynyl or CH₂aryl substituted by one or more groups Y₁;

wherein R₂ and R₃ may be bonded together to form a C₂₋₈ alkyl group;

R₄ is hydrogen, C₁₋₈ alkyl, CO₂C₁₋₈ alkylaryl substituted by one or more groups Y₁, CH₂aryl substituted by one or more groups Y₁, or CO₂C₁₋₈ alkyl;

Z is N, O or S; when Z is O or S, there is no R₅

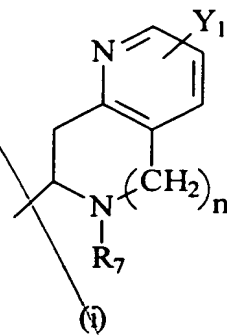
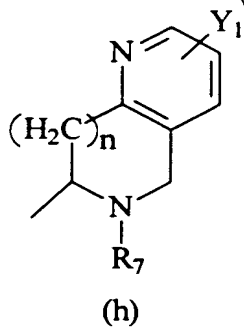
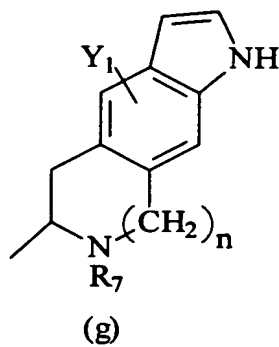
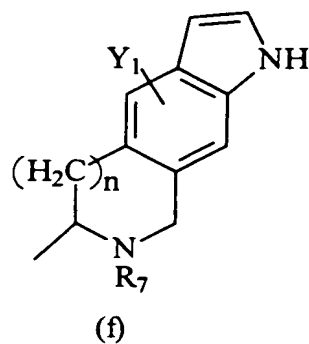
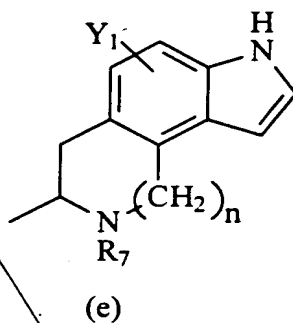
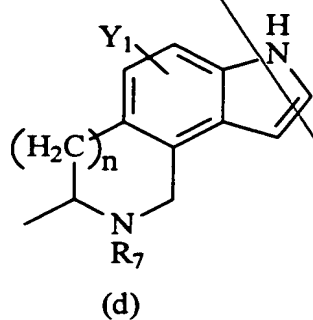
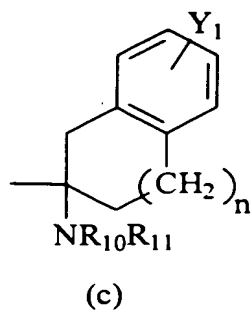
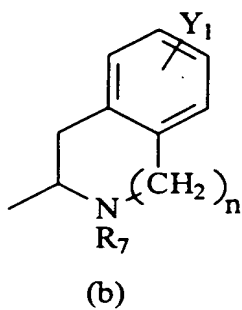
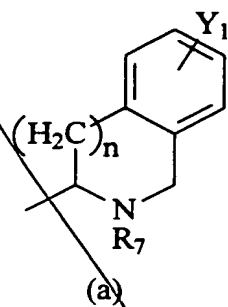
R₅ is H, C₁₋₈ alkyl, C₃₋₈ alkenyl, C₃₋₈ alkynyl, CH₂CO₂C₁₋₈ alkyl, CO₂C₁₋₈ alkyl or CH₂aryl substituted by one or more groups Y₁;

n is 0, 1, 2 or 3;

R₆ is a group selected from the group consisting of structures (a)-(bbb):

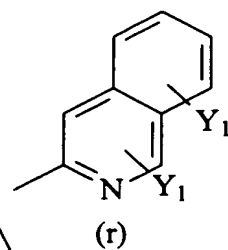
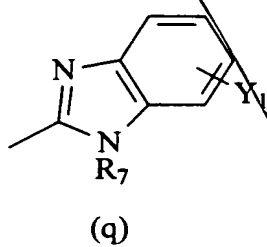
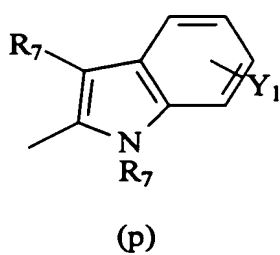
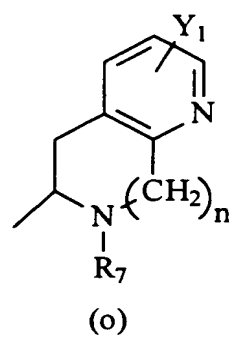
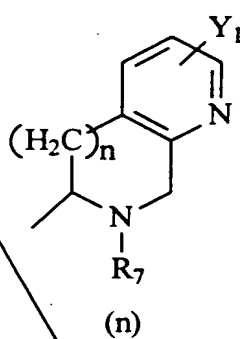
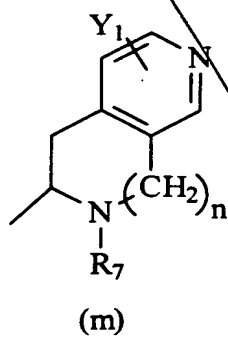
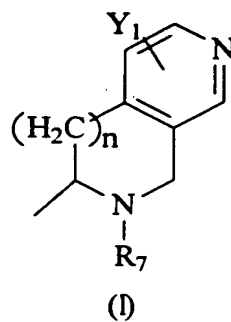
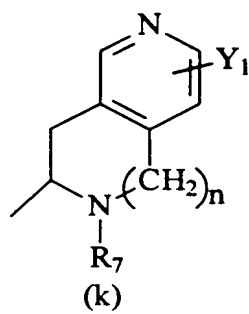
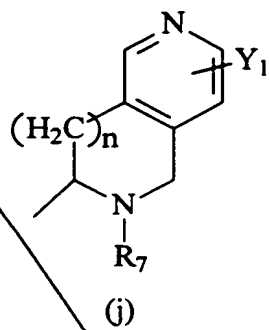
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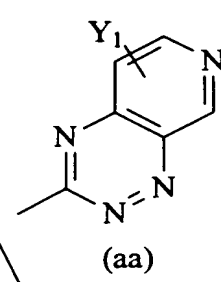
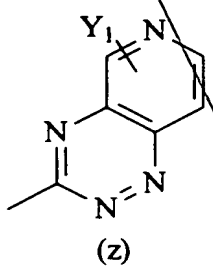
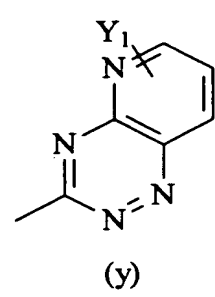
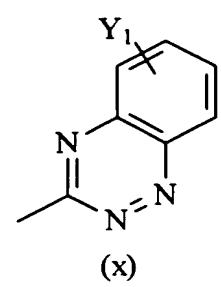
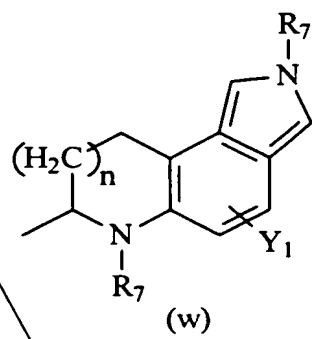
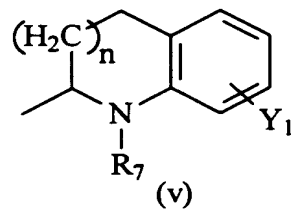
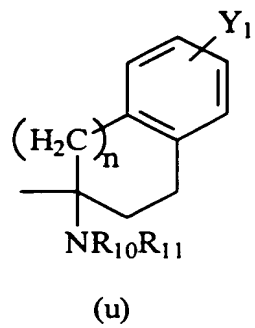
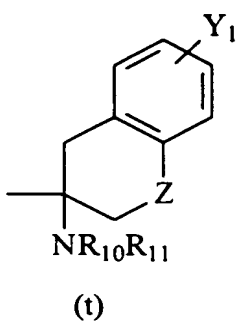
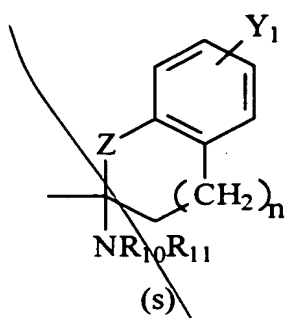
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TABLE 10-continued



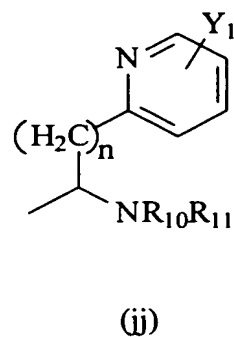
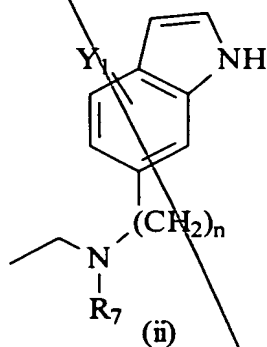
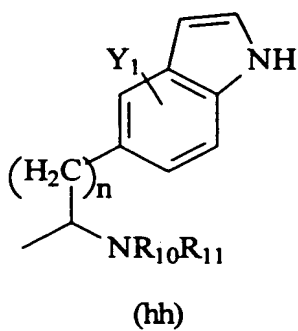
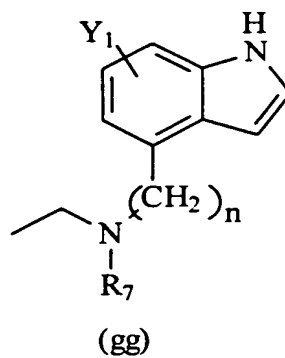
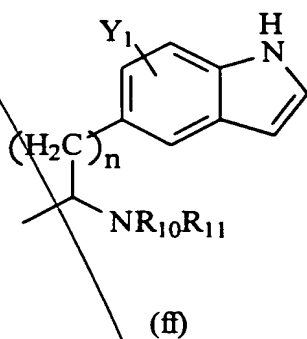
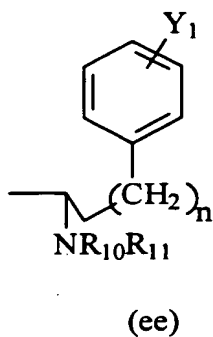
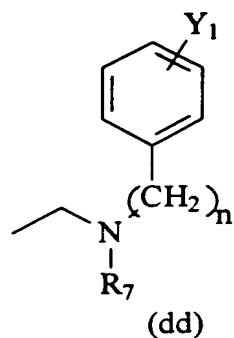
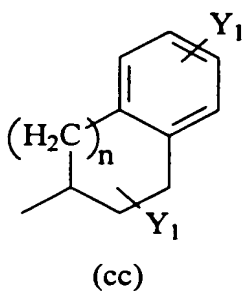
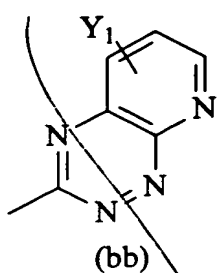


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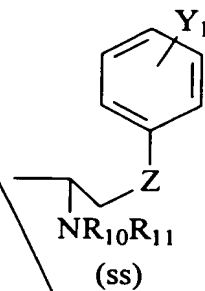
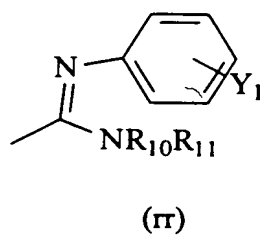
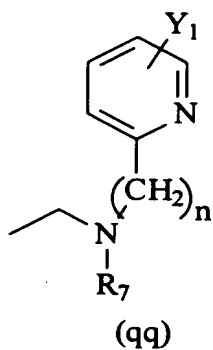
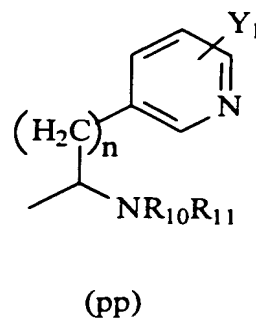
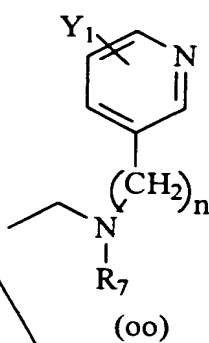
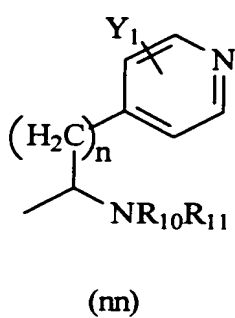
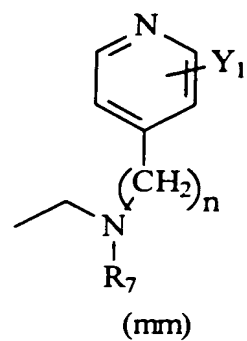
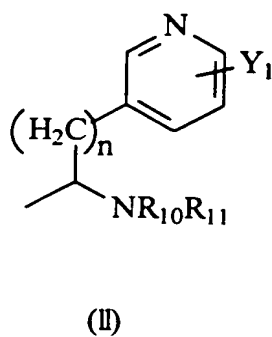
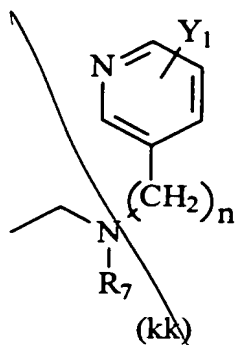
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FIG. 10

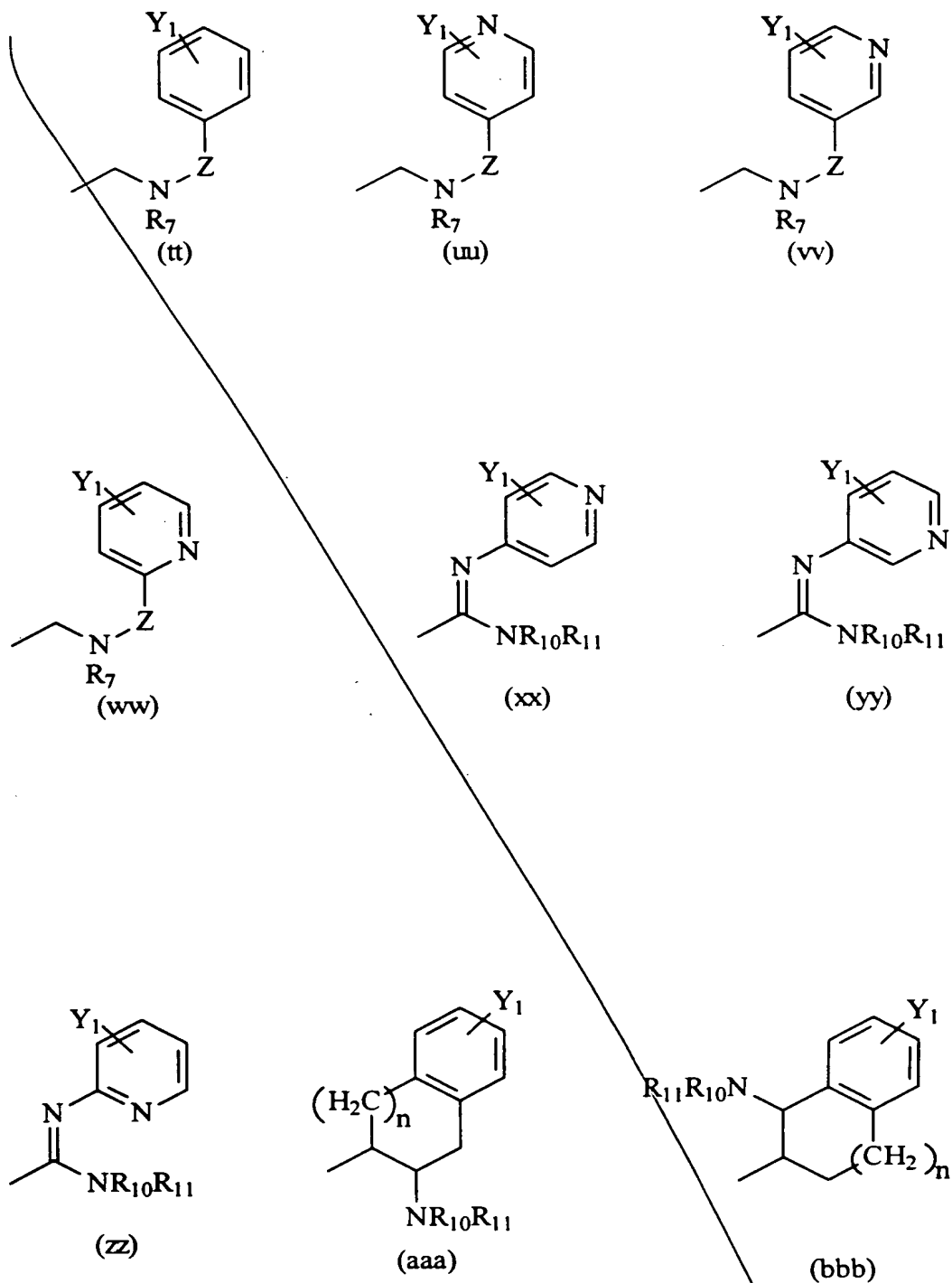


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X_1 is hydrogen, C_{1-8} alkyl, C_{3-8} alkenyl, C_{3-8} alkynyl;

X_2 is hydrogen, C_{1-8} alkyl, C_{3-8} alkenyl, C_{3-8} alkynyl;

or X_1 and X_2 together form $=O$, $=S$, $=NH$;

R_7 is H, C_{1-8} alkyl, CH_2 aryl substituted by one or more substituents Y_1 , $NR_{10}R_{11}$,

5 $NHCOR_{12}$, $NHCO_2R_{13}$, $CONR_{14}R_{15}$, $CH_2(CH_2)_nY_2$, $C(=NH)NR_{16}R_{17}$.

R_8 is H, C_{1-8} alkyl, CH_2 aryl substituted by one or more substituents Y_1 , $CONR_{13}R_{14}$,
 $CH_2(CH_2)_nY_2$;

R_9 is H, C_{1-8} alkyl, CH_2 aryl substituted by one or more substituents Y_1 , $CH_2(CH_2)_nY_2$;

R_{10} is H, C_{1-8} alkyl, CH_2 aryl substituted by one or more substituents Y_1 , $CH_2(CH_2)_nY_2$;

R_{11} is H, C_{1-8} alkyl, CH_2 aryl substituted by one or more substituents Y_1 , $CH_2(CH_2)_nY_2$;

R_{12} is H, C_{1-8} alkyl, CH_2 aryl substituted by one or more substituents Y_1 , $CH_2(CH_2)_nY_2$;

R_{13} is H, C_{1-8} alkyl, CH_2 aryl substituted by one or more substituents Y_1 , $CH_2(CH_2)_nY_2$;

R_{14} is H, C_{1-8} alkyl, CH_2 aryl substituted by one or more substituents Y_1 , $CH_2(CH_2)_nY_2$;

R_{15} is H, C_{1-8} alkyl, CH_2 aryl substituted by one or more substituents Y_1 , $CH_2(CH_2)_nY_2$;

15 R_{16} is H, C_{1-8} alkyl, CH_2 aryl substituted by one or more substituents Y_1 , $CH_2(CH_2)_nY_2$;

and

R_{17} is H, C_{1-8} alkyl, CH_2 aryl substituted by one or more substituents Y_1 , $CH_2(CH_2)_nY_2$
or a pharmaceutically acceptable salt thereof.

20 14. The pharmaceutical composition of claim 13, wherein said kappa opioid receptor antagonist is a compound of formula (I), wherein R_1 , R_4 , R_5 , Y_1 , Y_2 , Z , n , X_1 , X_2 , and R_7 - R_{17} are as indicated above;

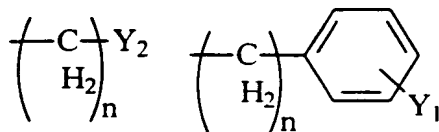
Y_3 is H;

R_2 and R_3 are each, independently, H, C_{1-8} alkyl, C_{3-8} alkenyl, C_{3-8} alkynyl, CH_2 aryl substituted by one or more substituents Y_1 ; and

25 R_6 is a group having a formula selected from the group consisting of structures (a)-(cc).

15. The pharmaceutical composition of claim 13, wherein said kappa opioid receptor antagonist is a compound of formula (I), wherein Y_1 , Y_2 , R_4 , R_5 , Z , n , X_1 , X_2 and R_8 - R_{15} are as indicated above;

30 R_1 is C_{1-8} alkyl,



Y₃ is H;

R₂ and R₃ are each, independently, H or C₁₋₈ alkyl, wherein R₂ and R₃ cannot both be H at the same time;

R₆ is a formula selected from the structures (a)-(r) shown above; and

R₇ is H, C₁₋₈ alkyl, CH₂aryl substituted by one or more substituents Y₁, NR₁₀R₁₁, NHCOR₁₂, NHCO₂R₁₃, CONR₁₄R₁₅, or CH₂(CH₂)_nY₂.

16. The pharmaceutical composition of claim 13, wherein said kappa opioid receptor antagonist is a compound of formula (I), wherein Y₁, Z, n, X₁, X₂ and R₈-R₁₅ are as noted above;

R₁ is C₁₋₈ alkyl;

Y₂ is H, CF₃, CO₂R₉, C₁₋₆ alkyl, NR₁₀R₁₁, NHCOR₁₂, NHCO₂R₁₂, CONR₁₃R₁₄, CH₂OH, CH₂OR₈, COCH₂R₉;

Y₃ is H;

R₂ and R₃ are each, independently, H or methyl, wherein R₂ and R₃ cannot both be H at the same time;

R₄ is H, C₁₋₈ alkyl, CO₂C₁₋₈alkyl, aryl substituted by one or more substituents Y₁ and the stereocenter adjacent to R₄ is in an (S) configuration;

R₅ is H, C₁₋₈ alkyl, CH₂CO₂C₁₋₈ alkyl;

R₆ is a group having a formula selected from the group consisting of structures (a)-(c) and (h)-(o); and

R₇ is H, C₁₋₈alkyl, CH₂aryl substituted by one or more substituents Y₁, NR₁₀R₁₁, NHCOR₁₂, NHCO₂R₁₃, CONR₁₄R₁₅, or CH₂(CH₂)_nY₂.

17. The pharmaceutical composition of claim 13, wherein said kappa opioid receptor antagonist is a compound of formula (I), wherein Y_1 , Z, n, X_1 , X_2 and R_8 - R_{14} are as indicated above;

R_1 is methyl,

Y_2 is H, CF_3 , CO_2R_9 , C_{1-6} alkyl, $NR_{10}R_{11}$, $NHCO_2R_{12}$, $NHCO_2R_{12}$, $CONR_{13}R_{14}$, CH_2OH , CH_2OR_8 , $COCH_2R_9$;

Y_3 is H;

R_2 and R_3 are each H or methyl, such that when R_2 is H, R_3 is methyl and vice versa;

R_4 is C_{1-8} alkyl, CO_2C_{1-8} alkyl, and the stereocenter adjacent to R_4 has a configuration of (S);

R_5 is H;

R_6 is a group having a formula selected from the group consisting of structures (a) and (b); and

R_7 is H, C_{1-8} alkyl, CH_2 aryl substituted by one or more substituents Y_1 or $CH_2(CH_2)_nY_2$.

18. The pharmaceutical composition of claim 13, wherein said kappa opioid receptor antagonist is a compound selected from formulae 14-21 of Fig. 1.

19. The pharmaceutical composition of claim 13, wherein said composition is an injectable composition.

20. The pharmaceutical composition of claim 13, wherein said composition is an orally administrable composition.

21. The pharmaceutical composition of claim 20, wherein said orally administrable composition is in a form selected from the group consisting of tablets, capsules, troches, powders, solutions, dispersions, emulsions and suspensions.

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